Remarks/Arguments

Claims 44-47 and 49-51 are pending in this application and are rejected on various grounds. Claim 47 has been canceled without prejudice or disclaimer. Claims 44-46 have been amended for clarity and to remove references to the "secreted" polypeptide and Claim 44 has been amended with the functional recitation "wherein, said nucleic acid sequences are amplified in lung or colon tumors". The foregoing amendments to the claims are of formal nature, and do not add new matter. The rejection to the presently pending claims are respectfully traversed.

Priority

Based on a positive result in the gene amplification assay, Applicants had previously asserted utility for the PRO317 polypeptide and believed that an effective filing date of September 10, 1998 was entitled to the instant application since the gene amplification data for PRO317 was first disclosed in the International application PCT/US98/18824, filed on 10 September, 1998 with a proper priority claim.

The Examiner acknowledged priority to the PCT/US00/04414 Application, filed February 22, 2000, but did not grant priority to other applications allegedly because, "the claimed subject matter is not supported in a manner provided by 35 U.S.C. §112, first paragraph (how to use requirement) in the earlier applications". The Examiner further indicated that the instant claims do not satisfy the utility requirement of 35 U.S.C. §101 or 35 U.S.C. §112, first paragraph for the polypeptide because "no information is provided regarding the level of expression, activity, or role in cancer of the PRO317 polypeptide". The Examiner cites Pennica *et al.* to show that DNA amplification is not always associated with overexpression of the gene product and consequently, contends that the asserted diagnostic utility for the PRO317 polypeptide constitutes carrying out further research for a "real world" use.

Applicants respectfully traverse these rejections and outline the reasons below for Applicants' assertion that the gene amplification assay provides adequate support for patentable utility of PRO317 polypeptides.

Utility Guidelines

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Arguments

A *prima facie* case of lack of utility has not been established

Applicants have asserted utility for PRO317 polypeptides based on gene amplification of the DNA encoding polypeptide PRO317 in 14 lung tumors and 6 colon tumors.

The Examiner bases the assertion, that increases in gene copy number do not reliably correlate with increased gene expression or polypeptide expression, on exemplary literature reports like Pennica *et al.*, and hence concludes that the PRO317 polypeptides lack utility.

According to the Examiner, Pennica *et al.* teaches that "*WISP*-2 DNA was amplified in colon cancer cell lines and in human colon tumors, but RNA expression was reduced (2- to >30-fold) in 79% of the tumors. This evidence indicates that DNA amplification is not always associated with overexpression of the gene product." However, the Examiner has not mentioned Pennica's results for the *WISP*-1 gene. Applicants draw attention to Pennica's showing that **a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene"in 84% of the tumors examined**. Thus, while Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches a correlation for the *WISP*-1 gene. Further, while Pennica's teachings are specific for the *WISP* family of genes, Pennica teaches nothing regarding such a lack of correlation in genes in general. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, in general. Accordingly, Applicants respectfully submit that based on Pennica's teachings alone, such a generalized teaching of the correlation between gene amplification and polypeptide over-expression has not been made.

Applicants further submit that it is generally well-understood in the art that DNA copy number influences gene expression. For example, Ornfoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Ornfoft *et al.* showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack *et al.,* who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that gene amplification correspondingly increases mRNA expression, in general.

Also enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding

protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm (as in Pennica) which are exceptions rather than the rule, in the vast majority of amplified genes, the combined teachings in the art exemplified by Orntoft *et al.,* Hyman *et al.* and Pollack *et al.,* and the Polakis declaration overwhelmingly teach that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the amplification data for the PRO317 gene, that the PRO317 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO317 proteins also has utility in the diagnosis of cancer and thus, one of skill in the art would know exactly how to use these molecules.

Claimed proteins would have diagnostic utility even if the protein were not overexpressed

Even assuming *arguendo* that, there is no correlation between gene amplification and increased mRNA/protein expression for PRO317, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant

> information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO317 polypeptide, for example, in detecting over-expression or absence of expression of PRO317. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Based on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides for the diagnosis of lung or colon cancer. Accordingly, PCT/US98/18824, filed on 10 September, 1998 also has utility and Applicants believe they are at least entitled to a priority date of **10 September, 1998**.

Thus, Applicants have demonstrated utility for the PRO317 polypeptide. Hence, these data clearly support a role of PRO317 as a lung or colon tumor marker. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

Claim Rejections – 35 USC § 102

Claims 44-47, 49-51 are rejected under 35 U.S.C.§ 102 (a) allegedly as being anticipated by Ruben (publication date, February 25, 1999).

Based on the discussions on utility and priority above, Applicants believe that they are at entitled to an effective filing date of at least September 10. 1998 for this application. Since Ruben et al. is dated after this effective filing date, it is not prior art under 102(a) and therefore, this rejection should be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 44, 47, 48, 50, 51 are rejected under 35 U.S.C. §112, second paragraph for being indefinite.

In view of the cancellation of claim 47 and references to "secreted" in the claims 44, 50 and 51, Applicants believe that this rejection should be withdrawn.

Information Disclosure Statement

Applicants submit that the PTO-1449 form filed in the IDS of 12/4/2003 refers individually to each Genbank gene accession number or Dayhoff protein accession number which correspond and were collectively referred to as "A1- Blast Results A1-A16, Genbank and A2- Blast Results B1-B9, Dayhoff" in the IDS of 3/14/2002. Applicants also enclosed the appropriate individual alignments in the IDS of 12/4/2003. Hence, Applicants had enclosed copies of the listed documents as per the requirements of 37 CFR 1.98(b). Applicants once again request the Examiner to reconsider the IDS of 12/4/2003.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C17). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: June 28, 2004

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